

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
2 June 2005 (02.06.2005)

PCT

(10) International Publication Number
WO 2005/049013 A1

(51) International Patent Classification⁷: **A61K 31/41**,
31/4965, 31/549, 45/06, A61P 3/10, 5/00, 5/18, 5/48, 5/50,
9/00, 9/02, 9/04, 9/10, 27/06, 43/00

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(21) International Application Number:
PCT/EP2004/012386

(22) International Filing Date:
2 November 2004 (02.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0325605.4 3 November 2003 (03.11.2003) GB

(71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **VASELLA, Daniel, Lucius** [CH/CH]; Novartis International AG, Lichtstrasse 35, CH-4056 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATIONS OF AT₁-ANTAGONISTS, AMILORIDE OR TRIAMTERINE, AND A DIURETIC.

(57) Abstract: The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising: (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and (ii) the diuretic amiloride or triameterine or a pharmaceutically acceptable salt thereof, and (iii) a further diuretic or a pharmaceutically acceptable salt thereof.

WO 2005/049013 A1

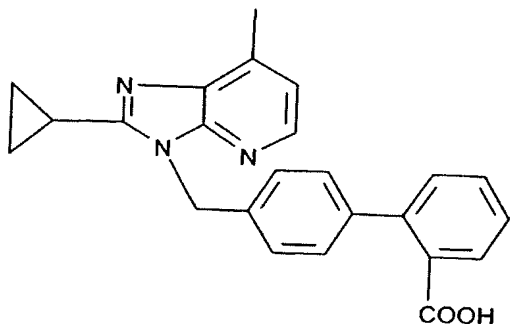
COMBINATIONS OF AT₁-ANTAGONISTS, AMILORIDE OR TRIAMETERINE, AND A DIURETIC

The invention relates to a combination, such as a combined preparation or pharmaceutical composition, respectively, comprising

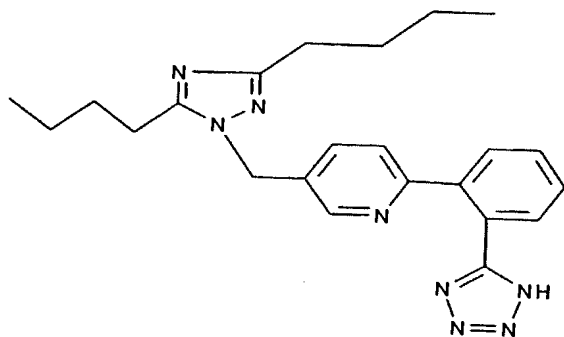
- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) amiloride or triameterine a pharmaceutically acceptable salt thereof and
- (iii) a thiazide diuretic or a pharmaceutically acceptable salt thereof.

AT₁-receptor antagonists (also called angiotensin II receptor antagonists or ARBs) are understood to be those active ingredients that bind to the AT₁-receptor subtype of angiotensin II receptor but do not result in activation of the receptor. As a consequence of the inhibition of the AT₁ receptor, these antagonists can, for example, be employed as anti-hypertensives or for treating congestive heart failure.

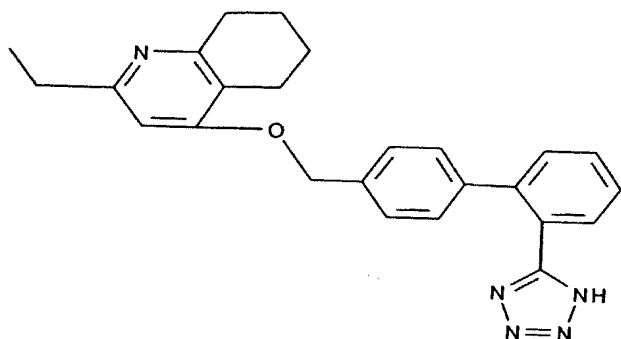
The class of AT₁ receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. For example, mention may be made of the compounds that are selected from the group consisting of valsartan (cf. EP 443983), losartan (cf. EP253310), candesartan (cf. 459136), eprosartan (cf. EP 403159), irbesartan (cf. EP454511), olmesartan (cf. EP 503785), tasosartan (cf. EP539086), telmisartan (cf. EP 522314), the compound with the designation E-1477 of the following formula



the compound with the designation SC-52458 of the following formula



and the compound with the designation the compound ZD-8731 of the following formula



or, in each case, a pharmaceutically acceptable salt thereof.

Preferred AT₁-receptor antagonist are those agents that have been marketed, most preferred is valsartan or a pharmaceutically acceptable salt thereof.

A preferred pharmaceutically acceptable salt of amiloride is the hydrochloride. Amiloride hydrochloride is the most preferred component (ii).

A thiazide diuretic is, for example, selected from the group consisting of chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon. Most preferred is hydrochlorothiazide.

Preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising

- (i) an AT₁-receptor antagonist or a pharmaceutically accepted salt thereof and
- (ii) amiloride or a pharmaceutically acceptable salt thereof and

- (iii) hydrochlorothiazide or a pharmaceutically acceptable salt thereof.

Preferred are combinations, such as a combined preparations or pharmaceutical compositions, respectively, comprising

- (i) valsartan or a pharmaceutically accepted salt thereof; and
- (ii) amiloride hydrochloride; and
- (iii) hydrochlorothiazide.

The structure of the active agents identified by generic or tradenames may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Life Cycle Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active agents and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both in vitro and in vivo.

The corresponding active ingredients or a pharmaceutically acceptable salts thereof may also be used in form of a solvate, such as a hydrate or including other solvents, used for crystallization.

The compounds to be combined can be present as pharmaceutically acceptable salts. If these compounds have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds having an acid group (for example COOH) can also form salts with bases.

The diuretics amiloride or triameterine or, in each case, a pharmaceutically acceptable salt thereof block the Na⁺ channels in the late distal tubules and collecting ducts by increasing the loss of sodium and chloride ions while reducing the excretion of potassium. It is known that the thiazide diuretics reduce the re-absorption of electrolytes from renal tubules, thereby increasing the excretion of sodium and chloride ions and consequently of water. The excretion of potassium is also increased by administering e.g. hydrochlorothiazide. The combination of amiloride, especially the hydrochloride thereof, or triameterine, respectively,

and a thiazide diuretic, for example, hydrochlorothiazide, increases the excretion of sodium and chloride ions while diminishing the kaliuretic effects.

All the more surprising is the experimental finding that the combined administration of the combination of

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) amiloride or a pharmaceutically acceptable salt thereof and
- (iii) a further diuretic or a pharmaceutically acceptable salt results not only in a beneficial, especially potentiation, preferably a synergistic, therapeutic effect, but also in additional benefits resulting from the combined treatment and further surprising beneficial effects compared to a monotherapy applying only one of the pharmaceutically active compounds used in the combinations disclosed herein.

In particular, all the more surprising is the experimental finding that the combination of the present invention results not only in a beneficial, especially a potentiation, preferably synergistic, therapeutic effect but also in additional benefits resulting from combined treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects on diseases and conditions as specified hereinafter.

Furthermore, a surprising effect of the combination of the present invention is the fact that a higher blood pressure lowering with lower dose of every component of the three therapy.

- Better potassium handling and homeostasis.

etter protection of the myocardium because of the haemodynamic effects of the three components and the protective effect of valsartan and amiloride. In fact, valsartan by blocking the detrimental actions of AT II on myocardial perfusion and remodeling post myocardial ischemia and necrosis and amiloride by blocking Na⁺/H⁺ exchanger that play a role in ischemia-reperfusion injury can protect the myocardium to a high extent in repetitive ischemia and acute myocardial infarction.

It can be shown by established test models and especially those test models described herein that the combination of the therapeutic agents selected from the group consisting of (i) to (iii) results in a more effective prevention or preferably treatment of diseases specified in the following. In particular, it can be shown by established test models and especially

those test models described herein that the combination of the present invention results in a more effective prevention or preferably treatment of diseases specified hereinafter.

If taken simultaneously, this results not only in a further enhanced beneficial, especially a synergistic, therapeutic effect, but also in additional benefits resulting from the simultaneous treatment such as a surprising prolongation of efficacy, a broader variety of therapeutic treatment and surprising beneficial effects, e.g. less increase of weight, on diseases and conditions associated with diabetes mellitus, for a number of combinations as described herein. Moreover, for a human patient, especially for elderly people, it is more convenient and easier to remember to take two tablets at the same time, e.g. before a meal, than staggered in time, i.e. according to a more complicated treatment schedule. More preferably, both active ingredients are administered as a fixed combination, i.e. as a single tablet, in all cases described herein. Taking a single tablet is even easier to handle than taking two tablets at the same time. Furthermore, the packaging can be accomplished with less effort.

The term "synergistic" as used herein means that the effect achieved with the methods and compositions of the present invention is greater than the sum of the effects that result from methods and compositions comprising the active ingredients of this invention separately.

The person skilled in the pertinent art is fully enabled to select a relevant and standard animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The pharmaceutical activities as effected by administration of representatives of the class of AT_1 -receptor antagonists or diuretics, respectively, or of the combination of active agents used according to the present invention can be demonstrated e.g. by using corresponding pharmacological models known in the pertinent art. The person skilled in the pertinent art is fully enabled to select a relevant animal test model to prove the hereinbefore and hereinafter indicated therapeutic indications and beneficial effects.

The beneficial effects on blood pressure can, for example, be demonstrated in the test model as disclosed in R.L. Webb et al., in J. Hypertension, 16:843-852, 1998.

Methods:

The combination according to the present invention comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof can be administered by various routes of administration but are tested in this example using a continuous infusion via subcutaneously-implanted osmotic minipumps. Each agent can be tested over a wide-range of dosages to determine the optimal drug level for each agent in combination to elicit the maximal response. For these studies, it is preferred to use treatment groups consisting of at least 6 animals per group. Each study is best performed in which the effects of the combination treatment group are determined at the same time as the individual components are evaluated. Although drug effects may be observed with acute administration (such as 1 day), it is preferable to observe responses in a chronic setting as shown below in which experiments were done over a two to three week observation period. The long-term study is of sufficient duration to allow for the full development of compensatory responses to occur and therefore, the observed effect will most likely depict the actual responses of the test system representing sustained or persistent effects. The effects on blood pressure depicted below represent a synergistic antihypertensive effect when the two agents are used in combination.

Statistical Analysis:

The combination therapy can be compared to that of the monotherapy groups by determining the maximum change in blood pressure or the area under the curve (AUC) for change in blood pressure over time in each of the treatment groups. All values are represented as the group mean \pm SEM. Statistical significance is obtained when $p < 0.05$. The AUC values for each of the treatment groups can be compared statistically using a one-way ANOVA followed by the appropriate post-hoc analysis, for example by performing a Tukey's test.

Results:

Blood pressure can be reduced to a similar degree using lower dosages of each of the components when given in combination than when the individual monotherapies are administered. An additional unexpected finding is that the blood pressure can be lowered to a greater extent with the combination than when the individual compound of formula (I) or a pharmaceutically acceptable salt thereof is given alone at a higher dosage.

These beneficial effects can, for example, be demonstrated in the test model as disclosed by G. Jeremic et al. in J. Cardiovasc. Pharmacol. 27:347-354, 1996.

For example, the valuable potential of the combination of the present invention for the prevention and treatment of myocardial infarction (including the post-myocardial infarction indication to delay the progression to congestive heart failure) can be found using the following test model.

Study design

In the study to be performed, permanent coronary artery occlusion (CAO) in rats is used as a model of acute myocardial infarction. The experiments are carried out with 5 treatment groups characterized by following features:

- sham-operated animals
- CAO + vehicle
- CAO + valsartan (val) or a pharmaceutically acceptable salt, thereof,
- CAO + amiloride (ami),
- CAO + hydrochlorothiazide (HCTZ);
- CAO + valsartan or a pharmaceutically acceptable salt thereof, + amiloride + hydrochlorothiazide.

During the study following variables are measured:

- infarct size
- LV chamber volume
- interstitial and perivascular collagen density in spared LV myocardium
- COL-I and COL-III protein content in spared LV myocardium by Western blot
- cardiomyocytes cross-sectional area and length in sections of LV myocardium
- plasma concentrations of renin and aldosterone
- urine concentration of sodium, potassium and aldosterone
- blood pressure in conscious animals
- LV and carotid blood pressure in anesthetized animals.

Methodology

Infarct size: Six μm -thick transverse histological sections of the left ventricle are stained with nitroblue tetrazolium and acquired by a B/W XC-77CE CCD video camera (Sony). The resulting image is processed on a KS 300 image analysis system (Carl Zeiss Vision) using a software specifically developed (Porzio *et al.*, 1995). A single operator blinded to treatment interactively defines the boundaries of the interventricular septum, and the infarcted area on each section is semiautomatically identified as the area of unstained ventricular tissue. The

software automatically calculates for each component of the ventricular section defined as the chamber, septum, infarcted area, infarcted LV wall and viable LV wall, a set of geometric parameters (Porzio *et al.*, 1995).

Histology: Hearts are fixed in situ, by retrograde perfusion with buffered 4% formaldehyde after arrest in diastole by i.v. injection of 0.5 M KCl. After fixation, the left ventricle (LV) and the free wall of the right ventricle are separately weighed; LV longer diameter is measured with a caliper. LV histological sections are stained with hematoxylin & eosin for qualitative examination and to quantify cardiomyocytes cross-sectional area with a semi-automated image analysis routine. Interstitial collagen deposition in LV is evaluated on Sirius red stained sections with a semi-automated image analysis routine (Masson *et al.*, 1998).

Collagen content in LV spared myocardium: LV tissue in the spared myocardium is homogenized, subjected to PAGE-SDS electrophoresis and electroblotted onto nitrocellulose membrane. The blots are exposed to primary antibodies, i.e. rabbit anti-rat collagen type I or type III antiserum (Chemicon). The primary antibodies are recognized by secondary antibodies conjugated to alkaline phosphatase (for collagen type I) or peroxidase (collagen type III).

Left ventricular chamber volume: LV chamber volume is determined in hearts arrested in diastole (KCl) and fixed in formalin under a hydrostatic pressure equivalent to the measured LV end-diastolic pressure. A metric rod is inserted into the LV to measure LV inner length. The transverse diameters of the LV chamber are measured in two 1-mm thick transverse sections near to the base and the apex of the ventricle (Jeremic *et al.*, 1996). The chamber volume is computed from an equation integrating transverse diameters and inner length.

Systemic and Left ventricular hemodynamics: A microtip pressure transducer (Millar SPC-320) connected to a recorder (Windograf, Gould Electronics) is inserted into the right carotid artery to record systolic and diastolic blood pressures. The pressure transducer is advanced into the LV to measure LV systolic (LVSP) and end-diastolic (LVEDP) pressures, the first derivative of LV pressure over time ($+dP/dt$) and heart rate.

Non-invasive blood pressure: Systolic blood pressure and heart rate are measured by the tail-cuff method (Letica LE 5002) in conscious rats.

Urine electrolytes, hormones: Rats are individually housed in metabolic cages and 24-h urine collected on 1 ml HCl 6N. Water intake is measured. Urine catecholamines are extracted on Bondelut C18 columns (Varian), separated by HPLC (Apex-II C18, 3 μ m, 50x4.5 mm analytical column, Jones Chromatography) and quantified with an electrochemical detector (Coulochem II, ESA) (Goldstein *et al.*, 1981). Plasma and urine aldosterone, and plasma angiotensin II are determined with specific radioimmunoassays (Aldoctk-2, DiaSorin and Angiotensin II, Nichols Diagnostics). Urine sodium and potassium are measured by flame photometry.

Sample size

10 animals analyzable in each treatment groups are sufficient to detect biologically significant differences. Only rats with an infarct size of at least 10% of the LV section area are included in the final analysis.

Endothelial dysfunction is being acknowledged as a critical factor in vascular diseases. The endothelium plays a bimodal role as the source of various hormones or by-products with opposing effects: vasodilation and vasoconstriction, inhibition or promotion of growth, fibrinolysis or thrombogenesis, production of anti-oxidants or oxidising agents. Genetically predisposed hypertensive animals with endothelial dysfunction constitute a valid model for assessing the efficacy of a cardiovascular therapy.

Endothelial disfunction is characterized by, for example, increased oxidative stress, causing decreased nitric oxide, increased factors involved in coagulation or fibrinolysis such as plasminogen activating inhibitor-1 (PAI-1), tissue factor (TF), tissue plasminogen activator (tPA), increased adhesion molecules such as ICAM and VCAM, increased growth factors such as bFGF, TGFb, PDGF, VEGF, all factors causing cell growth inflammation and fibrosis.

The treatment e.g. of endothelial dysfunction can be demonstrated in the following pharmacological test:

Material and methods

Male 20-24 week-old SHR, purchased from RCC Ltd (Fullingsdorf, Switzerland), are maintained in a temperature- and light-controlled room with free access to rat chow (Nafag

9331, Gossau, Switzerland) and tap water. The experiment is performed in accordance with the NIH guidelines and approved by the Canton Veterinary office (Bew 161, Kantonales Veterinäramt, Liestal, Switzerland). All rats are treated with the NO synthesis inhibitor L-NAME (Sigma Chemicals) administered in drinking water (50 mg/l) for 12 weeks. The average daily dose of L-NAME calculated from the water consumed was 2.5 mg/kg/d (range 2.1-2.7).

The rats can be divided into 5 groups: group 1, control (n = 40); Group 2, valsartan (val; n = 40); Group 3, amiloride (ami; n = 30); Group 4, hydrochlorothiazide (HCTZ; n = 30); Group 4, a combination (val-ami-HCTZ) (n = 30). The drugs are administered in drinking fluid. The doses to be used are selected from the work of Sweet et al. (1987) indicating significantly increased survival in rats with healed myocardial infarction. The pressor effect of Ang II at 1 mg/kg obtained in controls normotensive rats can be reduced after treatment with the compound of formula (I) in form of the hemi-fumarate (Gervais et al. 1999).

Body weight is measured every week. Systolic blood pressure and heart rate are recorded by tail cuff plethysmography 3 and 2 weeks before starting the study and at 2 weeks after drug administration. Urine is collected over a 24 hour period from rats kept in individual (metabolic) cages the week before starting treatment and at weeks 4 and 12 for volume measurement and protein, creatinine, sodium and potassium determination using standard laboratory methods. At the same time points, blood samples are withdrawn from the retro-orbital plexus (maximum 1 ml) for creatinine, Na⁺ and K⁺ assays.

Ten rats from each group are sacrificed at 4 weeks for collection of kidney and heart for morphological analysis. The remaining rats are sacrificed at 12 weeks. Cardiac and kidney weight is recorded. Terminal blood sampling is performed in 5 % EDTA at 4 (morphometry study) and 12 (end of the study) weeks for aldosterone, determination by radioimmunoassay using a DPC coat-a-count aldosterone-RIA kit (Bühlmann, Switzerland).

Statistical analysis:

All data are expressed as mean \pm SEM. Statistical analysis is performed using a one-way ANOVA, followed by a Duncan's multiple range test and a Newman-Keuls test, for comparison between the different groups. Results with a probability value of less than 0.05 are deemed statistically significant.

Results:

Even at non-blood pressure reducing doses, administration of the combination of the present invention leads to significant improvements in survival rates.

An improvement of regression of arteriosclerosis without effecting the serum lipid levels can, for example, be demonstrated by using the animal model as disclosed by H. Kano et al. in Biochemical and Biophysical Research Communications 259, 414-419 (1999).

That the compounds or combinations according to the present invention can be used for the regression of a cholesterol diet-induced atherosclerosis, can be demonstrated using the test model described, e.g., by C. Jiang et al. in Br. J. Pharmacol. (1991), 104, 1033-1037.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Design of Clinical Programs

A factorial design study in naïve or previously treated hypertensive patients is initiated in order to select the more appropriate dose(s) for subsequent use will be. The positive outcome of the selected dosage is based on synergy in blood pressure lowering, low incidence of side effects and better potassium handling of the combination. This study includes up to 120 patients in every cells of the explored doses of monotherapy and/or marketed combination of two of the three components of the triple combination.

Furthermore, non-responder study is carried out to show that the add on of a third agent of the combination may bring additional blood pressure lowering and more patients under control without increasing the side effects.

These study(s) show that this triple combination provides additional myocardial protection in patients having myocardial infarction, acute coronary syndrome, ischemic heart disease, myocardial revascularization at the acute or chronic phase of coronary occlusion. This claim is supported by clinical studies measuring markers of myocardial ischemia and injury such

as troponine T and I, CPK MB, myoglobine, as well as, markers of myocardial function such as ejection fraction, left ventricular dimensions and contractility measured by MRI, echography, scintigraphy etc. In addition measurement of myocardial salvage by technetium scintigraphy or other appropriate measure of myocardial salvage.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

Accordingly, the invention furthermore relates to a method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension,
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e)

glaucoma; furthermore

- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease;

comprising administering to a warm-blooded animal, including man, in need thereof a jointly effective amount of a combination of the renin inhibitor of formula (I) or a pharmaceutically acceptable salt thereof with at least one therapeutic agent comprising

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) amiloride or a pharmaceutically acceptable salt thereof and
- (iii) a further diuretic or a pharmaceutically acceptable salt thereof.

Furthermore, the present invention relates to the use of a combination comprising

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) amiloride or a pharmaceutically acceptable salt thereof and
- (iii) a further diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, or treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;
- (e) glaucoma; furthermore
- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease.

The invention furthermore relates to a pharmaceutical composition for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension, comprising administering the pharmaceutical composition of the present invention;

- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia;
 - (e) glaucoma; furthermore
 - (f) isolated systolic hypertension (ISH),
 - (g) diabetic retinopathy, and
 - (h) peripheral vascular disease;
- comprising
- ((i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
 - (ii) amiloride or a pharmaceutically acceptable salt thereof and
 - (iii) a further diuretic or a pharmaceutically acceptable salt thereof;
- and a pharmaceutically acceptable carrier.

Further benefits when applying the composition of the present invention are that lower doses of the individual drugs to be combined according to the present invention can be used to reduce the dosage, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects. This is in accordance with the desires and requirements of the patients to be treated.

Preferably, the jointly therapeutically effective amounts of the active agents according to the combination of the present invention can be administered simultaneously or sequentially in any order, separately or in a fixed combination.

The pharmaceutical composition according to the present invention as described hereinbefore and hereinafter may be used for simultaneous use or sequential use in any order, for separate use or as a fixed combination.

A further aspect of the present invention is a kit for the prevention of, delay of progression of, treatment of a disease or condition according to the present invention comprising

- (a) an amount of valsartan or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- (b) an amount of therapeutic agents (ii) and (iii), or, in each case, where appropriate, a pharmaceutically acceptable salt thereof in a second etc. unit dosage form; and
- (c) a container for containing said first, second etc. unit forms.

In a variation thereof, the present invention likewise relates to a "kit-of-parts", for example, in the sense that the components to be combined according to the present invention can be dosed independently or by use of different fixed combinations with distinguished amounts of the components, i.e. simultaneously or at different time points. The parts of the kit of parts can then e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention furthermore relates to a commercial package comprising the combination according to the present invention together with instructions for simultaneous, separate or sequential use.

These pharmaceutical preparations are for enteral, such as oral, and also rectal or parenteral, administration to homeotherms, with the preparations comprising the pharmacological active compound either alone or together with customary pharmaceutical auxiliary substances. For example, the pharmaceutical preparations consist of from about 0.1 % to 90 %, preferably of from about 1 % to about 80 %, of the active compound. Pharmaceutical preparations for enteral or parenteral, and also for ocular, administration are, for example, in unit dose forms, such as coated tablets, tablets, capsules or suppositories and also ampoules. These are prepared in a manner that is known per se, for example using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compound with solid excipients, if desired granulating a mixture which has been obtained, and, if required or necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

Preferred dosages for the active ingredients of the pharmaceutical combination according to the present invention are therapeutically effective dosages, especially those which are commercially available.

Normally, in the case of oral administration, an approximate daily dose of from about 1 mg to about 360 mg is to be estimated e.g. for a patient of approximately 75 kg in weight.

The dosage of the active compound can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition.

The pharmaceutical preparation will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet for oral treatment.

Valsartan, as a representative of the class of AT₁-receptor antagonists, will be supplied in the form of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 20 to about 320 mg, of valsartan which may be applied to patients. . A suitable dosage unit form may comprise 40 mg, 80 mg, 160 mg or 320 mg per dosage unit form. The application of the active ingredient may occur up to three times a day, starting e.g. with a daily dose of 20 mg or 40 mg of valsartan, increasing via 80 mg daily and further to 160 mg daily up to 320 mg daily. Preferably, valsartan is applied twice a day with a dose of 80 mg or 160 mg, respectively, each. Corresponding doses may be taken, for example, in the morning, at mid-day or in the evening. Preferred is b.i.d. administration.

Hydrochlorothiazide will be supplied in of suitable dosage unit form, for example, a capsule or tablet, and comprising a therapeutically effective amount, e.g. from about 5 mg to about 50 mg which may be applied to patients. Preferred doses per unit dosage form is 6,25 mg, 12,5 mg or 25 mg. The application of the active ingredient may occur up to three times a day.

The dosage of amiloride or triameterine, respectively, are those that are normally being used for mono-therapy, most preferably, the lower range of the prescribed doses. The application of the active ingredient may occur up to three times a day. A preferred dose per unit dosage form is 5 mg of amiloride hydrochloride.

Preferred are combinations, especially pharmaceutical compositions, comprising (i) a dose of valsartan selected from 40 mg, 80 mg, 160 mg and 320 mg of valsartan, (ii) 5 mg of

amiloride hydrochloride, and (iii) a dose of hydrochlorothiazide selected from 12.5 and 25 mg of hydrochlorothiazide.

Preferred are dosage unit forms or a single dosage unit form comprising

(i) a dose of valsartan selected from 40 mg, 80 mg, 160 mg and 320 mg of valsartan, (ii) 5 mg of amiloride hydrochloride, and (iii) a dose of hydrochlorothiazide selected from 12.5 and 25 mg of hydrochlorothiazide.

Especially preferred are low dose combinations.

The following examples illustrate the above-described invention; however, it is not intended to restrict the scope of this invention in any manner.

Formulation Example 1:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	80.00	
Microcrystalline cellulose/ Avicel PH 102	54.00	NF, Ph. Eur
Crospovidone	20.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.5	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	0.75	Ph. Eur/ NF
Magnesium stearate	2.00	NF, Ph. Eur
Coating		
Purified water	-	
DIOLACK pale red 00F34899	7.00	

Total tablet mass	167.00
-------------------	--------

^{*)} Removed during processing.

The film-coated tablet is manufactured e.g. as follows:

A mixture of valsartan, microcrystalline cellulose, crospovidone, part of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200, silicon dioxide and magnesium stearate is premixed in a diffusion mixer and then sieve through a screening mill. The resulting mixture is again pre-mixed in a diffusion mixer, compacted in a roller compacter and then sieve through a screening mill. To the resulting mixture, the rest of the colloidal anhydrous silica/colloidal silicon dioxide/Aerosile 200 are added and the final blend is made in a diffusion mixer. The whole mixture is compressed in a rotary tableting machine and the tablets are coated with a film by using Diolack pale red in a perforated pan.

Formulation Example 2:

Film-coated tablets:

Components	Composition Per Unit (mg)	Standards
Granulation		
Valsartan [= active ingredient]	160.00	
Microcrystalline cellulose/ Avicel PH 102	108.00	NF, Ph. Eur
Crospovidone	40.00	NF, Ph. Eur
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	5.00	NF, Ph. Eur
Blending		
Colloidal anhydrous silica / colloidal silicon dioxide / Aerosil 200	1.50	Ph. Eur/ NF
Magnesium stearate	4.00	NF, Ph. Eur
Coatings		
Opadry Light Brown 00F33172	10.00	

Total tablet mass	330.00
-------------------	--------

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 3:

Film-Coated Tablets:

Components	Composition Per Unit (mg)	Standards
Core: Internal phase		
Valsartan [= active ingredient]	40.00	
Silica, colloidal anhydrous (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [= Lubricant]	2.00	USP/NF
Crospovidone [Disintegrant]	20.00	Ph. Eur
Microcrystalline cellulose [= Binding agent]	124.00	USP/NF
External phase		
Silica, colloidal anhydrous, (Colloidal silicon dioxide) [= Glidant]	1.00	Ph. Eur, USP/NF
Magnesium stearate [Lubricant]	2.00	USP/NF
Film coating		
Opadry® brown OOF 16711 ¹⁾	9.40	
Purified Water ²⁾	-	
Total tablet mass	199.40	

¹⁾ The composition of the Opadry® brown OOF16711 coloring agent is tabulated below.

²⁾ Removed during processing

Opadry® Composition:

Ingredient	Approximate % Composition
Iron oxide, black (C.I. No. 77499, E 172)	0.50
Iron oxide, brown (C.I. No. 77499, E 172)	0.50
Iron oxide, red (C.I. No. 77491, E 172)	0.50
Iron oxide, yellow (C.I. No. 77492, E 172)	0.50
Macrogolum (Ph. Eur)	4.00
Titanium dioxide (C.I. No. 77891, E 171)	14.00
Hypromellose (Ph. Eur)	80.00

The film-coated tablet is manufactured e.g. as described in Formulation Example 1.

Formulation Example 4:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Microcrystalline cellulose	25.10
Crospovidone	13.00
Povidone	12.50
Magnesium stearate	1.30
Sodium lauryl sulphate	0.60
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540

Gelatin	74.969
Total tablet mass	209.50

The tablet is manufactured e.g. as follows:

Granulation/Drying

Valsartan and microcrystalline cellulose are spray-granulated in a fluidised bed granulator with a granulating solution consisting of povidone and sodium lauryl sulphate dissolved in purified water. The granulate obtained is dried in a fluidised bed dryer.

Milling/Blending

The dried granulate is milled together with crospovidone and magnesium stearate. The mass is then blended in a conical screw type mixer for approximately 10 minutes.

Encapsulation

The empty hard gelatin capsules are filled with the blended bulk granules under controlled temperature and humidity conditions. The filled capsules are dedusted, visually inspected, weightchecked and quarantined until by Quality assurance department.

Formulation Example 5:

Capsules:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	160.00
Microcrystalline cellulose	50.20
Crospovidone	26.00
Povidone	25.00
Magnesium stearate	2.60
Sodium lauryl sulphate	1.20
Shell	
Iron oxide, red (C.I. No. 77491, EC No. E 172)	0.123
Iron oxide, yellow (C.I. No. 77492, EC No. E 172)	0.123
Iron oxide, black (C.I. No. 77499, EC No. E 172)	0.245
Titanium dioxide	1.540

Gelatin	74.969
Total tablet mass	342.000

The formulation is manufactured e.g. as described in Formulation Example 4.

Formulation Example 6:

Hard Gelatine Capsule:

Components	Composition Per Unit (mg)
Valsartan [= active ingredient]	80.00
Sodium laurylsulphate	0.60
Magnesium stearate	1.30
Povidone	12.50
Crospovidone	13.00
Microcrystalline cellulose	21.10
Total tablet mass	130.00

Examples 7 to 11:

Example	7	8	9	10	11
Components	Compositio n per unit (mg)	Composit ion per unit (mg)	Composit ion per unit (mg)	Composit ion per unit (mg)	Composit ion per unit (mg)
Granulation					
Valsartan Drug Substance (DS)	80.000	160.000	40.000	320.000	320.000
Microcrystalline Cellulose (NF, Ph.Eur.)/ Avicel PH 102	54.000	108.000	27.000	216.000	216.000
Crospovidone (NF, Ph.Eur.)	15.000	30.000	7.500	80.000	60.000
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	1.500	3.000	0.750	3.000	6.000
Magnesium Stearate (NF, Ph.Eur.)	3.000	6.000	1.500	10.000	12.000
Blending					
Colloidal Anhydrous Silica (Ph. Eur.)/Colloidal Silicon Dioxide (NF)/Aerosil 200	---	---	---	3.000	-
Magnesium Stearate, NF, Ph.Eur.	1.500	3.000	0.750	8.000	6.000
Core Weight/mg	155.000	310.000	77.500	640.000	620.000
Coating	-	-	3.800	15.000	16.000

What is claimed is

1. A combination, such as a combined preparation or pharmaceutical composition, respectively, comprising
 - (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
 - (ii) the diuretic amiloride or triameterine or a pharmaceutically acceptable salt thereof, and
 - (iii) a further diuretic or a pharmaceutically acceptable salt thereof.
2. A combination according to claim 1, comprising
 - (i) valsartan or a pharmaceutically accepted salt thereof and
 - (ii) amiloride or a pharmaceutically acceptable salt thereof and
 - (iii) hydrochlorothiazide or a pharmaceutically acceptable salt thereof.
3. A combination according to claim 1, comprising
 - (i) valsartan and
 - (ii) amiloride hydrochlorid and
 - (iii) hydrochlorothiazide.
4. A pharmaceutical composition comprising a combination according to any one of claims 1 to 3.
5. A pharmaceutical composition for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of
 - (a) ^{hypertension} hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
 - (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
 - (c) endothelial dysfunction with or without hypertension,
 - (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore

- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease;

comprising

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) the diuretic amiloride or triameterine or a pharmaceutically acceptable salt thereof, and
- (iii) a further diuretic or a pharmaceutically acceptable salt thereof; and
- (iv) an auxiliary.

6. Use of a combination comprising

- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
- (ii) the diuretic amiloride or triameterine or a pharmaceutically acceptable salt thereof, and
- (iii) a further diuretic or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;
- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
- (c) endothelial dysfunction with or without hypertension,
- (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore
- (f) isolated systolic hypertension (ISH),
- (g) diabetic retinopathy, and
- (h) peripheral vascular disease.

7. A method for the prevention of, delay of progression of, treatment of a disease or condition selected from the group consisting of

- (a) hypertension, congestive heart failure, restenosis after percutaneous transluminal angioplasty, and restenosis after coronary artery bypass surgery;

- (b) atherosclerosis, insulin resistance and syndrome X, diabetes mellitus type 2, obesity, nephropathy, hypothyroidism, survival post myocardial infarction (MI), coronary heart diseases, hypertension in the elderly, familial dyslipidemic hypertension, increase of formation of collagen, fibrosis, and remodeling following hypertension (antiproliferative effect of the combination), all these diseases or conditions associated with or without hypertension;
 - (c) endothelial dysfunction with or without hypertension,
 - (d) hyperlipidemia, hyperlipoproteinemia, atherosclerosis and hypercholesterolemia, (e) glaucoma; furthermore
 - (f) isolated systolic hypertension (ISH),
 - (g) diabetic retinopathy, and
 - (h) peripheral vascular disease;
- comprising administering to a warm-blooded animal, including man, in need thereof jointly therapeutically effective amounts of
- (i) an AT₁-receptor antagonist or a pharmaceutically acceptable salt thereof, and
 - (ii) the diuretic amiloride or triameterine or a pharmaceutically acceptable salt thereof, and
 - (iii) a further diuretic or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No EP2004/012386				
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/41 A61K31/4965 A61K31/549 A61K45/06 A61P3/10 A61P5/00 A61P5/18 A61P5/48 A61P5/50 A61P9/00 A61P9/02 A61P9/04 A61P9/10 A61P27/06 A61P43/00				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
A	WO 01/28548 A (TEXAS HEART INSTITUTE; BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTE) 26 Apr11 2001 (2001-04-26) abstract page 2, line 25 - line 29 page 4, line 22 - page 5, line 16 claim 4 <div style="text-align: center;">----- -/--</div>	1-7		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.				
* Special categories of cited documents:				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>				
Date of the actual completion of the international search <div style="text-align: center;">11 February 2005</div>		Date of mailing of the international search report <div style="text-align: center;">28/02/2005</div>		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Taylor, G.M.</div>		

INTERNATIONAL SEARCH REPORT

International Application No

/EP2004/012386

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/40007 A (NOVARTIS AG; NOVARTIS-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT M.B.H; HEWIT) 23 May 2002 (2002-05-23) abstract page 1, line 1 - page 2, line 3 page 2 - page 3 page 7, line 5 - line 22 page 16, line 5 - page 19, line 2 page 22, line 6 claims 1-10	1-7
P, A	----- WO 03/097045 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; SHETTY, SURAJ, SHIVAPPA; WEBB, RAND) 27 November 2003 (2003-11-27) abstract page 1, paragraph 1 - page 2, paragraph 1 claims 1-16	1-7
P, A	----- US 2004/087484 A1 (SAHOTA PRITAM SINGH) 6 May 2004 (2004-05-06) abstract paragraph '0001! paragraph '0008! - paragraph '0010! paragraph '0018! paragraph '0024! paragraph '0035! paragraph '0042! claims 1-18	1-7
P, A	----- DÜSING, R; LEHNERT, H.: "Diabetogenic effect of antihypertensive treatment: primum nil nocere" NEPHROL DIAL TRANSPLANT, vol. 19, no. 3, March 2004 (2004-03), pages 531-534, XP002317306 the whole document -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP2004/012386

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0128548	A	26-04-2001	AU 8026200 A	30-04-2001
			WO 0128548 A1	26-04-2001
			US 6323226 B1	27-11-2001
WO 0240007	A	23-05-2002	AU 2368002 A	27-05-2002
			BR 0115411 A	17-08-2004
			CA 2428647 A1	23-05-2002
			CN 1474690 T	11-02-2004
			WO 0240007 A1	23-05-2002
			EP 1341533 A1	10-09-2003
			HU 0301841 A2	29-09-2003
			JP 2004513920 T	13-05-2004
			MX PA03004358 A	19-08-2003
			NO 20032233 A	16-05-2003
			PL 361404 A1	04-10-2004
			SK 5842003 A3	04-11-2003
			ZA 200303497 A	28-04-2004
WO 03097045	A	27-11-2003	CA 2486144 A1	27-11-2003
			WO 03097045 A1	27-11-2003
US 2004087484	A1	06-05-2004	AU 2636502 A	11-06-2002
			CA 2430924 A1	06-06-2002
			EP 1353727 A2	22-10-2003
			JP 2004514703 T	20-05-2004
			WO 0243807 A2	06-06-2002
			US 2002107236 A1	08-08-2002